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ARTICLE

Managing hypercholesterolaemia

SUMMARY

Hypercholesterolaemia is one of the most common conditions treated by clinicians in Australia. Low-density lipoprotein cholesterol (LDL-C) plays a causal role in the development and progression of atherosclerosis and cardiovascular disease.

Every 1 mmol/L reduction in LDL-C concentration is associated with a 21 to 25% reduction in the relative risk of prospective atherosclerotic cardiovascular events, and emerging evidence suggests this benefit increases over time.

Absolute cardiovascular risk assessment identifies patients likely to derive the most benefit from lowering LDL-C concentration, and helps determine the intensity of their treatment regimens and targets.

Optimal management of LDL-C may require combination treatment with multiple classes of drugs.

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Introduction

Hypercholesterolaemia is one of the most common conditions managed in clinical practice. A large-scale survey in 2011 to 2012 revealed that approximately one-third of the Australian population have elevated total cholesterol concentrations (more than 5.5 mmol/L).[1] Based on the Australian Burden of Disease Study 2018, hypercholesterolaemia contributed to an estimated 2.7% of the total burden of disease and up to 37% of the coronary heart disease burden.[2]

This article explores the causal links between low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides in atherosclerotic cardiovascular disease (CVD), and discusses elevated and normal LDL-C concentrations, and approaches to lowering LDL-C concentration.

Lipids, lipoproteins and the lipid profile

Lipids such as cholesterol and triglycerides are insoluble in plasma and are transported throughout the body by circulating lipoproteins. There are 6 major classes of lipoproteins (Box 1). Each of these carry both cholesterol and triglycerides in varying proportions; low-density lipoprotein (LDL) carries the majority of cholesterol and very low-density lipoprotein (VLDL) carries the majority of triglyceride.

The terms 'cholesterol', 'LDL' and 'LDL-C' are sometimes conflated. LDL concentrations are generally not measured; instead, the amount of cholesterol contained in LDL particles (i.e. LDL-C) is reported.

Total cholesterol is made up of the LDL-C, HDL-C and a proportion of the triglyceride concentration. LDL-C is usually the dominant contributor to the total cholesterol concentration; however, focusing on the total cholesterol concentration may overlook other useful information in a full lipid profile. An elevation in total cholesterol, if not separated into its constituents, may instead reflect significant hypertriglyceridaemia, which confers an elevated risk of cardiovascular events but is less likely to respond to drugs that lower LDL-C concentration. Hence, clinicians are encouraged to discuss the importance of each component of the lipid profile with their patients: HDL-C, LDL-C, total cholesterol and triglycerides.

Box 1 Major classes of lipoproteins

- chylomicrons
- very low-density lipoproteins (VLDL)
- intermediate-density lipoproteins
- low-density lipoproteins (LDL)
- high-density lipoproteins (HDL)
- lipoprotein(a)

Causal links between lipids and atherosclerotic cardiovascular disease

LDL-C and atherosclerotic cardiovascular disease

LDL-C is a causal risk factor for atherosclerotic CVD.[3] This has been established from several lines of evidence including Mendelian randomisation (natural selection) studies, large prospective cohorts, and randomised placebo-controlled clinical trials of multiple drugs that lower LDL-C concentration.[4] These data all support the same conclusion: a dose-

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dependent, log-linear association exists between LDL-C concentration and the prospective risk for atherosclerotic CVD events.[5]

The underlying biology has become increasingly clear. Retention of LDL particles by macrophages within the arterial wall leads to oxidation and generation of an inflammatory milieu, resulting in accumulation of foam cells, fatty streaks and atherosclerotic plaques. Unchecked, especially in the presence of other traditional risk factors (e.g. tobacco smoking, diabetes, hypertension), these plaques can become unstable, leading to occlusive events such as myocardial infarction, stroke and limb ischaemia. Although lowering LDL-C concentration is the cornerstone of atherosclerotic CVD prevention, these observations reinforce the need for comprehensive management of risk factors in people with elevated LDL-C concentrations.[6-8]

HDL-C and atherosclerotic cardiovascular disease

Epidemiological data show an inverse correlation between HDL-C concentrations and incident atherosclerotic CVD. Low HDL-C concentrations are more common among people who are overweight or obese, and those who smoke tobacco or adopt a sedentary lifestyle.[9] Therapies that have successfully raised HDL-C concentrations in clinical trials have not yet been shown to reduce cardiovascular events.[10] Thus, while HDL-C concentrations continue to play a role in CVD risk calculators (low concentrations are associated with increased risk; high concentrations are associated with protection against CVD), therapies that raise HDL-C concentrations (such as niacin) are no longer recommended.

Triglycerides and atherosclerotic cardiovascular disease

Independent associations have been established between triglyceride concentration and coronary artery disease risk.[11] Mendelian randomisation (natural selection) studies suggest this risk is mediated by triglyceride-laden apolipoprotein B–containing lipoproteins (especially VLDL and remnant cholesterol) in a manner that is analogous to apolipoprotein B–containing LDL particles.[12] However, the degree to which lowering the triglyceride concentration reduces atherosclerotic CVD risk remains unknown.

Therapies that modestly lower triglyceride concentrations, such as fibrates (approximately 25% reduction), have not been shown to impart consistent cardiovascular benefits.[13] Trials of omega-3 fatty acids in patients with elevated triglyceride concentrations have produced conflicting results.[14] In the REDUCE-IT trial, icosapent ethyl (an ethyl ester of eicosapentaenoic acid) was shown to significantly reduce cardiovascular events,[15] while in the STRENGTH trial, a carboxylic acid formulation of eicosapentaenoic acid and docosahexaenoic acid in similar patients was neutral.[16] The discordant findings may reflect different trial designs, patient populations, baseline therapy, or type or dose of omega-3 fatty acid; however, any benefit appears to be independent of lowering the triglyceride concentration.[14] Based on positive results from the REDUCE-IT trial,[15] icosapent ethyl has been approved by the Therapeutic Goods Administration (TGA) to reduce the risk of cardiovascular events in adults on statins who are at high CVD risk, specifically people with elevated triglyceride concentrations (1.7 mmol/L or higher) plus either established CVD, or diabetes and at least one other CVD risk factor.

Compounds capable of more potent lowering of triglyceride concentration (by approximately 70%) are in clinical development and may answer the question as to whether lowering triglyceride concentration definitively impacts cardiovascular outcomes.[17]

Approach to checking the lipid profile

A person's lipid profile should be evaluated as part of CVD risk assessment. The *2023 Australian Guideline for assessing and managing CVD risk* recommends individuals without known CVD should have their CVD risk assessed from age 45 to 79 years, but in people with diabetes this should occur from age 35 years. In First Nations people, individual CVD risk factors should be assessed from age 18 to 29 years, and CVD risk assessed from age 30 years.[18]

For people not starting lipid-lowering therapy, CVD risk assessment (and thus lipid profile) should be repeated at least every 2 years for those deemed intermediate risk (5% to less than 10%), and every 5 years for those deemed low risk (less than 5%). For people starting or changing their dose of lipid-lowering therapy, a lipid profile can be repeated as early as 6 weeks later.

Non-fasting blood samples may be used for lipid screening; however, these need to be interpreted with caution in the presence of elevated triglycerides (more than 4 mmol/L), in which case a fasting sample should subsequently be drawn. Thus, fasting samples are generally recommended where possible and are required for an evaluation of temporal change.

Elevated LDL-C concentration

Most individuals develop mild to moderate hypercholesterolaemia in the context of a genetic susceptibility plus secondary contributors. Secondary contributors may include a diet rich in saturated

fats, a sedentary lifestyle, or drugs known to elevate cholesterol (e.g. thiazide diuretics, amiodarone). Laboratory testing should also include assessment of glycated haemoglobin to exclude diabetes (often associated with elevated triglyceride concentrations); thyroid function to exclude hypothyroidism (associated with fewer LDL receptors and thus decreased clearance of LDL-C);[19] and standard biochemistry (kidney and liver function tests) to exclude nephrotic syndrome and liver disease.

Severe elevation in LDL-C concentration (more than 5 mmol/L) or total cholesterol concentration (more than 7.5 mmol/L), especially in people with a family history of premature atherosclerotic CVD (first-degree male relative younger than 55 years or first-degree female relative younger than 65 years), should prompt consideration of a genetic cause such as familial hypercholesterolaemia. Australian data on the epidemiology of familial hypercholesterolaemia are sparse, although a recent estimate suggests a prevalence of approximately 1 in 250 people,[20] with up to 90% potentially unaware of their condition. In a person with severe elevation of LDL-C or total cholesterol concentration, assessment should include searching for a family history of premature atherosclerotic CVD. Clinical examination may reveal evidence of cholesterol deposition on the eyelids, extensor tendons or cornea. Clinical criteria (e.g. the Dutch Lipid Network score) can identify familial hypercholesterolaemia in adults without the need for genetic testing; however, genetic testing may be useful to inform screening of biological relatives of people with confirmed familial hypercholesterolaemia ('cascade screening'),[20] or if more detailed risk stratification is required.

The decision to treat elevated LDL-C should take into account absolute CVD risk, LDL-C concentration, and consideration of secondary causes of dyslipidaemia (which should be addressed, if possible).

'Normal' LDL-C concentration and when to lower it

Small cholesterol-laden LDL particles freely enter and exit the arterial wall at LDL-C concentrations of 0.5 to 1 mmol/L,[21] making it difficult to know what represents a 'normal' LDL-C concentration. There are likely genetic and other determinants of whether LDL particles are retained in the arterial wall, but higher numbers of circulating LDL particles increase the likelihood of retention.[22] Imaging studies have shown plaques are less likely to progress with LDL-C concentrations below 1.8 mmol/L.[23] In addition, abundant data support the notion that 'lower is better' – every 1 mmol/L reduction in LDL-C concentration is associated with a 21 to 25% reduction in the relative risk of atherosclerotic cardiovascular events,[5] and emerging evidence suggests this benefit increases over time.[24]

The question is not whether lowering LDL-C concentration reduces CVD risk, as the data indicate this occurs in a linear and predictable fashion, but whether medicine adherence, tolerability and the societal cost of medicines challenge the expected benefit of the risk reduction.

Absolute CVD risk assessment provides a construct to determine the magnitude of benefit at the patient level. By calculating a person's absolute risk of atherosclerotic CVD, the impact of proportionate reductions in LDL-C concentration can be modelled, and the expected absolute risk reduction and number needed to treat can be determined. A higher baseline risk leads to a greater absolute risk reduction. A shared decision-making approach is favoured here; for example, some people may view an absolute risk reduction from 7% to 5% as clinically meaningful, while others may view an absolute risk reduction from 20% to 15% as marginal. In the *2023 Australian Guideline for assessing and managing CVD risk*, lipid- and blood pressure–lowering therapy is recommended for people without established CVD and a 10% or more absolute 5-year risk of a cardiovascular event, but may also be considered for people with intermediate risk using a shared decision-making approach.[18]

Treatment targets for LDL-C concentration

As coronary artery disease is a continuum of subclinical and clinical disease and an initial atherosclerotic CVD event can be life threatening, most guidelines have evolved away from a false dichotomy of 'primary' and 'secondary' prevention and instead focus on multivariable risk stratification.

The *2023 Australian Guideline for assessing and managing CVD risk* addresses people without established disease and does not explicitly mention treatment targets for elevated LDL-C concentration.[18] In contrast, the American[25] and European[26] guidelines are relatively consistent in assigning treatment targets by estimated CVD risk. People with the highest absolute risk (e.g. multiple atherosclerotic vascular territories, multiple clinical events) should have the lowest LDL-C concentration treatment targets (e.g. below 1.4 mmol/L and 50% or more reduction in LDL-C concentration from baseline), consistent with more intensive treatment regimens. People with fewer traditional risk factors have a lower absolute risk and thus have more permissive LDL-C concentration treatment targets (e.g. below 3.0 mmol/L) and less intensive treatment regimens.

Approaches to lowering LDL-C concentration

Several nonpharmacological and pharmacological approaches may be used (often in combination) to lower LDL-C concentration; these are listed in Table 1. Importantly, the benefits of lowering LDL-C concentration occur proportionately to the baseline risk and are independent of the mode of reduction.[5]

Lifestyle modifications

Multiple professional societies recommend a 'heart-healthy' diet, although the exact composition of this is variable and lacks rigorous evidence. The National Health and Medical Research Council's *Australian dietary guidelines* are being updated and are due for release in 2024.[34] Contemporary cardiovascular guidance from the European Society of Cardiology suggests that lower LDL-C concentration can be achieved by food choices that include wholegrain cereals, vegetables, legumes, fish, poultry without skin, and avoidance of trans-saturated fats.[26] Other healthy lifestyle modifications include weight loss (for people who are overweight or obese) and regular physical activity (e.g. 30 minutes of moderate-intensity exercise most days of the week).[18] While these modifications yield modest reduction in LDL-C concentration (approximately 5%) (Table 1), their beneficial effects on overall cardiovascular health, blood pressure and diabetes are more pronounced.

Statins

Statins are the first-line drugs for reducing LDL-C concentration as they are inexpensive, effective and well tolerated. Most guidelines categorise statins

Table 1 Interventions for lowering low-density lipoprotein cholesterol (LDL-C) concentration

		Intervention or drug [NB1]	Approximate reduction in LDL-C concentration [NB2]
Lifestyle modifications		replacing saturated fat with unsaturated fat	5 to 15%[27]
		increasing the intake of plant sterols to more than 1.5 g/day	5 to 10%[28]
		losing approximately 10% body weight	5 to 10%[29]
		increasing aerobic exercise	10%[30]
		consuming the DASH diet	5%[28]
Statins	**low intensity**	simvastatin 10 mg pravastatin 10 to 20 mg fluvastatin 20 to 40 mg	up to 30%[25]
	moderate intensity	atorvastatin 10 to 20 mg rosuvastatin 5 to 10 mg simvastatin 20 to 40 mg pravastatin 40 to 80 mg fluvastatin 40 mg twice daily or 80 mg daily	30 to 49%[25]
	high intensity	atorvastatin 40 to 80 mg rosuvastatin 20 to 40 mg	50% or more [25]
Niemann-Pick C1–like transporter (cholesterol absorption) inhibitor		ezetimibe 10 mg	15 to 20%[31]
PCSK9 inhibitors	**monoclonal antibody**	evolocumab 140 mg by subcutaneous injection every 2 weeks, or 420 mg once a month	50 to 70%[32]
	small interfering RNA	inclisiran 300 mg [NB3] by subcutaneous injection initially, then repeated at 3 months, then every 6 months	50%[33]

DASH = Dietary Approaches to Stop Hypertension; PCSK9 = proprotein convertase subtilisin/kexin type 9
NB1: Drug route of administration is oral and frequency is daily, unless specifically stipulated.
NB2: Expected reduction in LDL-C concentration may vary by baseline concentration and concomitant therapy.
NB3: Inclisiran solution for injection contains inclisiran sodium 300 mg, equivalent to inclisiran 284 mg.

and their respective doses into low-, moderate- or high-intensity therapy, indicating their expected effect on lowering LDL-C concentration (Table 1). While the notion 'lower is better', achieved by 'maximally tolerated statin therapy', applies for those at the highest risk for atherosclerotic CVD events, the intensity of statin therapy should be chosen according to an individual's baseline and target LDL-C concentrations, while considering potential adverse effects at higher doses.

For reasons not completely understood, statins can cause muscle damage. Muscle damage may be a mild form of myopathy (serum creatine kinase [CK] concentration more than 3 times the upper limit of normal) that occurs at a rate of 1 in 1000 patient–years, or as potentially lethal rhabdomyolysis (serum CK concentration more than 10 times the upper limit of normal), occurring at a rate of 1 in 100,000 patient–years.[26] While rare, the incidence of both myopathy and rhabdomyolysis is increased by concomitant use of drugs that inhibit the cytochrome P450 3A4 hepatic enzymes responsible for metabolising most statins (except pravastatin and rosuvastatin). Myopathy-inducing drug interactions are more common in people using simvastatin (especially at doses higher than 80 mg daily, which is no longer recommended) or statins in combination with gemfibrozil (but not other fibrates like fenofibrate).[35-37]

In contrast to myopathy, mild muscle aches without a high serum CK concentration are reported in as many as 10 to 20% of statin users in observational literature, and frequently result in down-titration and nonadherence.[38] This rate is far in excess of what has been seen in randomised, placebo-controlled clinical trials, in which only 1 in 15 muscle-related adverse effects were attributable to statins, and less frequently resulted in drug discontinuation.[39] An 'N-of-1' randomised trial showed that many muscle symptoms arise from the 'nocebo' or 'drucebo' effect[40] rather than from the statin, effects that are likely perpetuated by negative perception and misinformation around statins in the community.[41]

Several strategies can be tried to improve statin adherence, including discontinuation and rechallenge with another statin (e.g. pravastatin may have fewer adverse effects), or discontinuation and restarting at a lower dose (e.g. alternate daily or even weekly), followed by cautious up-titration.[42] Up to 70% of patients previously considered statin intolerant may tolerate a statin when these strategies are used.[43] While vitamin D supplementation has not been shown to impact statin adherence,[44] severe vitamin D deficiency is known to cause muscle aches and, if present, should be corrected to avoid misattributing these symptoms to statins.[45]

Before starting a statin, a baseline assessment of liver biochemistry and serum CK concentration is recommended, although routine monitoring of these is not required.

Most patients at high risk of CVD will not achieve lower treatment targets for LDL-C concentration on monotherapy, even at the highest intensity statin therapy.[46] A 2- or 3-drug approach may be required to achieve optimal management.

Ezetimibe

Ezetimibe is the only approved Niemann-Pick C1–like transporter (cholesterol absorption) inhibitor and is considered the second-line drug for reduction of LDL-C concentration when added to a statin, or in people with statin intolerance. It is reimbursed for these indications by the Pharmaceutical Benefits Scheme (PBS), and is available in fixed-dose combinations with atorvastatin and simvastatin, and as a combination pack with rosuvastatin, to facilitate adherence.

Ezetimibe can lower LDL-C concentration by approximately 20% as monotherapy, or approximately 15% when added to moderate- or high-intensity statin therapy (Table 1). In a double-blind, randomised trial, proportionate to its modest lowering of LDL-C concentration, ezetimibe added to simvastatin resulted in a 7% relative risk reduction in the primary end points of cardiovascular death, nonfatal myocardial infarction, or hospitalisation for unstable angina or revascularisation.[31] The main adverse effect of ezetimibe is flatulence, but this is tolerable in most patients and rarely causes discontinuation.

Proprotein convertase subtilisin/kexin type 9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) indirectly regulates serum LDL-C by targeting the LDL receptors for degradation. Inhibiting or binding circulating PCSK9 prevents the destruction of LDL receptors and allows them to be recycled to the hepatocyte surface, thereby decreasing serum LDL-C concentration.

Several approaches to targeting PCSK9 currently exist. At the time of writing, there are 3 injectable PCSK9 inhibitors approved by the TGA.[47] Evolocumab and alirocumab are monoclonal antibodies, whereas inclisiran is a long-acting, small interfering RNA (siRNA). Each drug is approved for treatment of patients at high risk of CVD who do not achieve LDL-C targets; however, at the time of writing, only evolocumab and alirocumab are reimbursed by the PBS. Evolocumab is PBS-funded for initial or continuing treatment; in December 2022 the PBS criteria for starting therapy were expanded to better

reflect contemporary guidelines (threshold for initiation: LDL-C above 1.8 mmol/L rather than above 2.6 mmol/L), and to allow GPs to start the drug in consultation with a specialist. Alirocumab is PBS-funded for continuing treatment (or switching within the same class) only.

Evolocumab and alirocumab reduce LDL-C concentration by approximately 60% in combination with maximally tolerated statin therapy, while inclisiran reduces LDL-C concentration by approximately 50% (Table 1). Clinical trials of evolocumab have shown favourable effects on atheroma burden[48] and high-risk plaque features,[49] which explains its positive impact on clinical outcomes (i.e. fewer cardiovascular events proportionate to reduction in LDL-C concentration).[32,50] Evolocumab and alirocumab are administered subcutaneously every 2 weeks or once a month. Inclisiran interferes with the production of PCSK9 in the liver. It is long acting, facilitating a 6-month dosing interval (after an initial 'booster'), which may improve adherence to therapy in the long term.[33]

As patents for PCSK9 inhibitors expire and new compounds emerge, competition for therapies that reduce LDL-C concentration will shape reimbursement decisions. An oral PCSK9 inhibitor is in clinical development.

Emerging lipid-lowering drugs

Recent guideline updates have focused on identifying patients at high risk of CVD for whom lower LDL-C targets are recommended. Given LDL-C targets are difficult to achieve with monotherapy, optimal management of LDL-C is likely to need a multidrug approach (analogous to hypertension or diabetes) for many patients. Thus, there remains an unmet need for novel agents capable of potent LDL-C lowering, particularly for those who cannot tolerate guideline-recommended doses of statins. The following approaches are in various stages of development.

Bempedoic acid inhibits the same cholesterol biosynthesis pathway as statins and reduces LDL-C concentration by approximately 20%.[51] A large clinical trial showed that in patients unable to take statins at guideline-recommended doses, bempedoic acid reduced myocardial infarction, stroke, coronary revascularisation and CVD-related mortality by 13%; however, the drug is not yet approved for use in Australia.[52]

Obicetrapib, a cholesteryl ester transfer protein inhibitor, reduces LDL-C concentration by approximately 50% and is currently undergoing late-phase clinical development.[53]

Gene-based therapies that knock down PCSK9 production in the liver and reduce LDL-C concentration by up to 60% have been successfully described in nonhuman primates and are undergoing first-in-human trials.[54]

Conclusion

The causal role of LDL in atherosclerosis has cemented the benefit of reducing LDL-C concentration in atherosclerotic CVD risk reduction. Absolute risk assessment is central to a shared decision-making process and informs treatment intensity and LDL-C concentration targets. Statins remain the first-line drugs for management of hypercholesterolaemia as they are inexpensive, effective and generally well tolerated. Ezetimibe offers a safe (albeit less effective) alternative for individuals who are intolerant to statins, or as add-on treatment to maximally tolerated statins when LDL-C concentration targets are not achieved. Strict reimbursement criteria currently limit the broad adoption of PCSK9 inhibitors, but as new drugs enter the market and patents expire, their use is expected to grow. <

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